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REVIEW ARTICLE

Evaluation of Risk Factors for Alzheimer's Disease in Elderly East Africans

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ABSTRACT: A number of biological risk factors have been implicated for Alzheimer's disease (AD). The investigation of prevalence rates of AD in crosscultural populations has much potential in validating these factors. We previously assessed brain amyloid β (Aβ) protein deposition and other lesions associated with AD as possible markers for preclinical AD in elderly nondemented East Africans. In further analysis, we demonstrate that 17–19% of elderly East African subjects without clinical neurological disease exhibited neocortical Aβ deposits and minimal neurofibrillary changes at necropsy that was qualitatively and quantitatively similar to that in an age-matched elderly control sample from Cleveland, OH. Aβ deposits varied from numerous diffuse to highly localized neuritic plaques and were predominantly reactive for the longer Aβ_{42} species. In parallel studies, we evaluated another recently implicated factor in AD, the apolipoprotein E genotype. We found relatively high frequencies of the apolipoprotein E-ϵ4 allele in elderly nondemented East Africans. The frequencies were comparable to those in other African populations but higher than in subjects from developed countries. Our limited study suggests that elderly East Africans acquire cerebral lesions found in AD subjects but the apolipoprotein E-ϵ4 allele may not be a highly specific factor for the disease among East Africans. © 1997 Elsevier Science Inc.

KEY WORDS: Alzheimer's disease, Apolipoprotein E, Cerebral amyloid, Dementia, East Africa, Epidemiology.

INTRODUCTION

Previous epidemiological studies have implied comparable prevalence rates of Alzheimer's disease (AD) within populations of developed countries in the West [2,5,11]. However, there is little information on the frequency of age-related dementias in the developing countries [5,6,14]. Geographical variations in the frequency of age-associated dementias between crosscultural populations have been suggested but they remain largely unconfirmed [2,41]. Indeed, the search for rigorous risk factors would be greatly expedited if there was a concerted effort to identify populations with significantly lower or higher rates of the disease [20,30]. Information about life style factors, including diet, head injury, medication use, medical history, alcohol use, education, occupation, smoking, and recreational activities, can be invaluable for comparison between different cultural, language, and ethnic groups [11]. The incidence of AD in indigenous populations of Africa particularly needs to be known. Isolated reports have suggested that dementias including AD exist in Africa [5,9,31] but systematic hospital surveys or community-based studies have only been recently initiated [14].

RISK FACTORS FOR AD IN AFRICA

Current advances in epidemiological studies have defined the statistics of the prevalence, incidence and risk factors for AD [5]. Important factors, aside from apolipoprotein (apoE; *APOE*)-ϵ4, include age, female gender, low years of education, low level of occupational attainment, family history of dementia, head trauma, small head size, and lower levels of premorbid recreational activities [11]. Recent evidence also implicates peripheral vascular disease in late-onset AD [17,40]. However, protective factors that have been demonstrated include history of smoking, use of nonsteroidal antiinflammatory drugs, or estrogen replacement therapy [43]. In the past 5 years there has been an increasing number of AD studies in African Americans [14,21]. Many of these pertain to care-giver factors and social concerns but are important for the management of AD. Biological factors in African Americans involving blood pressure, lipid metabolism, salt handling, and cerebrovascular disease are also of considerable interest. Environmental concerns regarding diet, high altitude living, education, occupation, and pollutants can also be productively addressed in crosscultural studies after eliminating dementias caused by acquired immunodeficiency syndrome (AIDS) or alcohol-related encephalopathy [13,24]. The gathering of information from crosscultural studies can allow us to move forward in identifying mechanisms by which the risk or protective factors operate [11,41].

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TABLE 1

Aβ PLAQUES AND ALZHEIMER TYPE OF LESIONS IN NEOCORTEX OF ELDERLY SUBJECTS FROM EAST AFRICA AND OHIO, USA

Origin of sample* (Age Range in Years)	No. With Lesions/Total	Age (Years); Sex	Aβ Plaques†	NFT‡	CAA
Nairobi, Kenya (45–70)	7/36 (19%)	<64; 3M/F	++	++	+
		>65; 3M	+++	++	++
Dar es Salaam, Tanzania (45–83)	3/14 (17%)	48/M	++	+	±
		55/M	+++	+	++
Cleveland, Ohio (48–84)	4/20 (20%)	62/F	++	+	+
		>65; 2M/F	++	+	++

These results constitute additional analysis (unpublished observations) to that reported previously [28] and were obtained by methods essentially as described [18].

* East African sample included only black indigenous subjects, whereas the Cleveland sample was 100% Caucasian.

† Aβ plaque immunoreactivity was graded by examination of two to five sections stained with antibodies to Aβ peptides. $A\beta_{42}$ positive plaques were more abundant than $A\beta_{40}$. Sections from the four neocortical lobes and hippocampus were examined. Many plaques were also thioflavin S–positive.

‡ NFT were assessed in the hippocampus. Occasional NFT, neuritic plaques, and neurites were noted in the temporal and frontal cortex. Degree of severity is represented in increasing order as low (+) to high (+++). Abbreviations: CAA, cerebral amyloid angiopathy; NFT, neurofibrillary tangles.

Current community-based studies and necropsy surveys in West [30,31] and East Africa [24] suggest dementia to be rare in black Africans [30,31]. One of the earlier studies involving house-to-house screening of elderly Nigerians suggested that dementia of the AD type was rare as determined by the DSM-III-R criteria [29]. However, in a more recent large community-based study AD was found to be represented in Ibadan, Nigeria, but at relatively low prevalence [14]. It is suggested that AD is likely to surface in certain countries as industrialization, the prevalence of vascular disease and life expectancy increase [4,13,32]. Compared to developed countries, the prevalence of cardiovascular disease has been considered to be insignificant in indigenous Africans [26], but increases in incidence rates of heart disease and hypertension have been predicted [24] and recently demonstrated in certain groups in step with demographic transition [13]. In view of recent evidence suggesting that vascular disease including stroke [13,36,40] appear to be strong risk factors for AD, it might be anticipated that AD will also rise in African populations.

NECROPSY STUDIES AND PRECLINICAL AD

In addition to other accompanying lesions, Aβ protein deposits are critical to the pathological diagnosis of AD. Cerebral amyloid β (Aβ) deposition in the elderly is widely considered part of pathological aging and possibly a precursor to AD [8,10,25]. A simple approach to identifying preclinical AD or early signs of AD in different populations is to screen brain tissue from routine necropsies that can bear much information and can usually be obtained with minimal cost. Using a similar strategy to that of the Nigerian investigators [32], we examined brains from aging East Africans for the distribution of Aβ protein and other lesions associated with typical AD [28]. We also screened brain tissues from a group of age-matched subjects with no known neurological disease from Cleveland, OH, for comparison. Subjects died of various causes including ischemic heart disease, liver disease, carcinoma, bronchopneumonia, and sudden death due to cardiac arrest, asphyxia, and traffic accidents. Available information from the charts or informants indicated that none of the subjects had shown clinical signs of dementia or had been previously admitted for neurological or psychiatric evaluation. Where information was available, most of the subjects had been city dwellers and were from various occupations including subsistence farmers, peasants, businessmen, housewives, and general factory workers [24,28].

In contrast to the rarity of AD in elderly Nigerians, supported by both epidemiological and necropsy findings [29,32], we reported in a previous study [28] that the occurrence of cerebral Aβ deposits and neurofibrillary changes was apparently similar in elderly East Africans as in a sample of nondemented aged subjects from Cleveland [28]. In additional analysis presented here (Table 1), we showed that seven brains from the 36 Kenyan samples demonstrated distinct Aβ deposits immunostained by all the Aβ antibodies. Two of these brains revealed a strikingly high density of compact and diffuse plaques distributed in neocortical layers 3–5 and evident in the frontal, temporal, and parietal cortices (Table 1). One of the brains also showed severe cerebral amyloid angiopathy (CAA) involving both meningeal and intraparenchymal vessels. Among the 14 Tanzanian subjects examined, 3 showed plaques that were readily apparent upon Aβ immunocytochemistry (Table 1). One of these had numerous diffuse deposits in the frontal cortex and the other exhibited few compact plaques in the temporal cortex, with many meningeal as well as intraparenchymal vessels showing light but positive Aβ immunoreactivity. In general, diffuse Aβ deposits were more abundant than compact ones in all 10 African samples. Adjacent tissue sections revealed that many of the plaques were thioflavin S-positive. In serial sections from all the subjects, we also noted that most of the $A\beta_{42}$ and $A\beta_{40}$-containing lesions, including vascular deposits, were immunoreactive for the amyloid-associated factors apoE, serum amyloid P, and complement C3. The presence of these markers suggested qualitative similarities between the African samples and those described with typical AD. All of the East African findings were similar to the lesions comprising Aβ deposits and few neurofibrillary tangles (NFT) found in the samples from Cleveland. Whereas these observations suggested that the percent of subjects exhibiting age-related amyloid lesions were comparable in the Kenyan, Tanzanian, and Ohioan (Cleveland) samples, it was interesting that the African subjects with the Aβ deposits were a few years younger than the group with similar cerebral lesions from Cleveland (Table 1). Our findings thus far suggest that Aβ deposition in brains of elderly East Africans is qualitatively similar to those found in the nondemented aging and AD subjects in American communities and other Western populations [10]. We were particularly intrigued to find that some of the brains exhibited a relatively high density of Aβ-immunoreactive

TABLE 2

COMPARISON OF *APOE* E4 ALLELE FREQUENCIES IN VARIOUS POPULATIONS FROM DEVELOPED AND AFRICAN COUNTRIES

Study*	Source of Patients (Age range or mean ±SD in years)	Normal Subjects†		
		ϵ2	ϵ3	ϵ4
Adroer et al. [1] Spain	Community and hospital samples (71.5 ± 10.29)	7.3 68 alleles	89.7	2.9
Benjamin et al. [3] UK	Hospital samples (age not indicated)	7 110 alleles	78	14.5
Corder et al. [7] USA	Duke University Medical Center (60–86)	10.7 486 alleles	74.3	15.0
Frisoni et al. [12] Italy	Hospital samples; Elderly samples (69.2 ± 3.6)	10 102 alleles	72	18
Hendrie et al. [14] USA (IN) African Americans	Community samples (78.2 ± 6.1)	9.3 108 alleles	76.8	13.9
Hong et al. [16] China	Hospital samples; Elderly samples (73.2 ± 5.9)	7.0 114 alleles	85.1	7.9
Kamboh et al. [19] USA (PA) African Americans	Community samples (Young samples)	3.4	70.6	26
Mayeux et al. [22] USA (NY) African Americans	Community samples (66.1 ± 8.9)	— 122 alleles	—	33
Mayeux et al. [23] USA (NY) African Americans	Community samples (72.9 ± 9.1)	—	—	28
Maestre et al. [21] USA (NY) African Americans	Community samples (74 ± 5.8)	2 114 alleles	74	24
Nakagawa et al. [27] Japan:Japanese	Hospital samples (55–76)	8 200 alleles	82	11
Osuntokun et al. [33] Africa: Nigerian Blacks	Community samples (77.6 ± 10.4)	7.7 78 alleles	71.8	20.5
Poirier et al. [34] Canada	McGill/Clinical Center in Montreal (75.8 ± 9.6)	12.2 142 alleles	77	8.8
Sandholzer et al. [37] Africa: South African Bushmen	Community sample	—	—	37.0
Sepehrnia et al. [39] Africa: Nigerian Blacks	Community samples (age range unknown)	2.7 730 alleles	67.7	29.6
West et al. [42] USA	Massachusetts General Hospital (77.6 ± 12.7)	8.6 468 alleles	82.9	8.6

* Unless otherwise stated, populations in developed countries were Caucasian. Source, ages of subjects, and allele frequencies are given if known.

† In most of these studies, APOE ϵ4 allele frequencies in demented patients diagnosed with AD were in the range 17–45%. For comparison, we previously reported the *APOE*-ϵ4 allele frequency of 15% in a necropsy series of non-neurological control subjects [35]. Abbreviations: IN, Indiana; NY, New York; PA, Pennsylvania.

plaques comparable to that described in some preclinical AD subjects [8].

APOE AS A GENETIC RISK FACTOR FOR AD IN AFRICA?

The *APOE* gene, mapped on chromosome 19, is considered to have more widespread effects than any other genetic factor implicated in AD [7]. The gene is controlled by three codominant alleles, *APOE* E2, E3, and E4, resulting in a polymorphism of six possible genotypes. The E4/E4 genotype carries the highest risk for AD, and the E4 allele frequency is increased two to three times in AD subjects compared to the frequency in general population. *APOE*-ϵ4 is also associated with earlier onset of disease and greater severity of Aβ protein deposition in brain parenchyma and vessel walls [35]. The mechanism(s) by which *APOE* exerts its effect on AD is unknown, but thus far several scenarios involving tau phosphorylation, Aβ protein aggregation, and lipid mobilization have been proposed. Interestingly, Mayeux and colleagues have also suggested that *APOE* effects may be caused by another genetic locus, close to the *APOE* gene, which is in linkage disequilibrium with the *APOE* gene [21–23].

It is now undisputed that *APOE*-ϵ4 is an important factor in AD. Several recent studies have confirmed the distribution of the three alleles in different populations (Table 2). Although the first few studies suggested *APOE*-ϵ4 frequency to be high among African Americans [19,22,23], it appears that this may not be a general phenomenon in American populations [15]. However, it has been reported that the frequency of *APOE*-ϵ4 allele is relatively high among nondemented Nigerians [19,33,39] and other African populations such as the Bushmen of Southern Africa [37].

To assess whether the *APOE*-ϵ4 allele was a genetic factor for AD among elderly East Africans, we examined the distribution of *APOE* genotypes by analyzing DNA from blood samples of Tanzanian and Kenyan Africans. The frequencies of the three

TABLE 3

FREQUENCY OF *APOE* ALLELES IN NONDEMENTED ELDERLY TANZANIANS AND KENYANS

Origin (Institution) (No. of Subjects)	Age Group (No of Alleles)	ϵ2 %	ϵ3 %	ϵ4 %
Dar es Salaam, Tanzania* (Muhimbili) (143)	<65years (152)	14.5	67.8	17.8
	≥65years (134)	14.2	61.2	24.6
	Total (286)	14.3	64.7	21.0
Nairobi, Kenya* (Avenue Hospital) (61)	<65years (62)	13.0	50.0	37.0
	≥65years (60)	5.0	68.0	27.0
	Total (122)	9.0	59.0	32.0

* The analysis (unpublished observations) showed there were four $\epsilon2/\epsilon2$ (2.8%) and three $\epsilon4/\epsilon/4$ (2.1%) genotypes in the Tanzanian sample, whereas no $\epsilon2/\epsilon2$ (0%) and three $\epsilon4/\epsilon4$ (4.9%) genotypes in the Kenyan sample. Blood was collected by venepuncture from subjects of African origin attending clinic at the Muhimbili Medical Centre, Dar es Salaam, Tanzania and Avenue Hospital, Nairobi. Samples were genotyped for *APOE* according to the modified method of Wenham et al., as described by Premkumar et al. [38]. Comparisons of the distribution of genotype and allele frequencies in the various groups were made by Pearson's δ^2 and Fisher's exact tests.

common *APOE* alleles are shown in Table 3. As for the necropsies, age, geographic and ethnic origin were the only known criteria used in the random selection of cases. The hospital records were also checked for major neurological and psychiatric diseases. Subjects suspected of dementia were not included in the analysis and were further evaluated using a modified minimental score exam in Swahili (J. Sayi et al., unpublished observations). The nondemented subjects were analyzed by age and grouped into those below 65 years of age and those above 65 years. These preliminary results showed that while *APOE*-ϵ3 allele was the most common, surprisingly high frequencies of the ϵ4 allele were evident in both the Kenyan and Tanzanian subjects. There were no significant differences in allele frequencies between the two age groups (Table 3).

Our study showed that the nondemented elderly Tanzanians and Kenyans exhibit relatively high *APOE*-ϵ4 allele frequencies compared to normal aging subjects from Western countries including some African-Americans (Table 2). These findings are comparable to those from Nigeria [33] and most of the small cohorts reported by Mayeux et al. [22,23]. However, the *APOE*-ϵ4 allele frequencies previously reported in elderly African-Americans from Indiana were lower than those found in Tanzanians [15]. We also noted relatively high frequencies of the *APOE*-ϵ2 allele in our sample (cf. Tables 2 and 3) compared to previous observations in Western populations [7,41]. Our recent preliminary studies suggest a lack of correlation in *APOE*-ϵ4 allele distributions between nondemented and putatively demented Tanzanians over 65 years of age (R.N. Kalaria et al., unpublished findings). Although we have not determined the causes of dementia among the demented group, these observations appear consistent with similar high frequencies of the *APOE*-ϵ4 allele in both the demented and normal elderly Nigerians [33].

CONCLUSIONS

There is little information on incidence of AD in indigenous populations of Africa. We have considered certain currently recognized risk factors for AD in an attempt to elucidate the occurrence of the disorder among elderly East Africans. Our observations suggest the distribution of cerebral Aβ deposition, CAA, and neurofibrillary changes in aging East Africans to be qualitatively similar to that in an equivalent sample of elderly controls from Cleveland, OH. These findings do not necessarily provide prevalence rates of preclinical AD, but they imply that elderly East Africans are unlikely to escape AD as it is known in developed countries. Increasing incidence of vascular disease and numbers in the aging population would likely enhance the manifestations of the disease.

Our preliminary results also suggest that elderly East Africans, particularly Kenyans, with no clinical AD or dementia exhibit relatively high *APOE*-ϵ4 allele frequencies compared to normal aging subjects from Western countries including the Indiana African-Americans. These results are similar to those reported in a recent study [33] in Nigerians in which a lack of relationship between *APOE*-ϵ4 allele frequency and Alzheimer type of dementia was noted. The observations support the notion that inheritance of *APOE*-ϵ4 allele may not necessarily be a strong risk factor in some populations in Africa.

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